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## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P26531ACMUMCM		<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/GB 03/04128	International filing date (day/month/year) 19.09.2003	Priority date (day/month/year) 19.09.2002	
International Patent Classification (IPC) or both national classification and IPC G01N33/66			
Applicant THE UNIVERSTITY OF ULSTE et al.			
<p>1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 3 sheets.</p>			
<p>3. This report contains indications relating to the following items:</p> <p>I <input checked="" type="checkbox"/> Basis of the opinion</p> <p>II <input type="checkbox"/> Priority</p> <p>III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p>IV <input type="checkbox"/> Lack of unity of invention</p> <p>V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p>VI <input type="checkbox"/> Certain documents cited</p> <p>VII <input type="checkbox"/> Certain defects in the international application</p> <p>VIII <input type="checkbox"/> Certain observations on the international application</p>			
Date of submission of the demand  14.04.2004		Date of completion of this report  08.11.2004	
Name and mailing address of the international preliminary examining authority:   European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016		Authorized Officer  Jenkins, G  Telephone No. +31 70 340-2608  	

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. **PCT/GB 03/04128**

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, Pages**

1-19 as originally filed

**Claims, Numbers**

1-11 received on 11.10.2004 with letter of 11.10.2004

**Drawings, Sheets**

1/2-2/2 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).  
☐ the language of publication of the international application (under Rule 48.3(b)).  
☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority in written form.  
☐ furnished subsequently to this Authority in computer readable form.  
☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.  
☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:  
☒ the claims, Nos.: 12-14  
☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
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International application No. PCT/GB 03/04128

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

**see separate sheet**

**Re Item V**

**Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

- 1 The following document D1 is referred to in this communication; the numbering will be adhered to in the rest of the procedure:

D1: MCKILLOP ET AL: 'Production and characterization of specific antibodies for evaluation of glycated insulin in plasma and biological tissues.', J ENDOCRINOL, October 2001, vol. 167, no. 1, pages 153 to 163.

**2 NOVELTY**

- 2.1 The subject-matter of claims 1-11 is new in the sense of Article 33(2) PCT, since the prior art does not disclose using glycated insulin as a biomarker for: monitoring progression of diabetes towards an increased severity, prediction of individuals at risk of developing diabetes, or diagnosing the early onset of diabetes when glucose levels are still within the normal range.

**3 INVENTIVE STEP**

- 3.1 The subject-matter of claims 1-11 is considered inventive under Article 33(3) PCT.
- 3.1.1 The subject-matter of claim 1 is considered inventive under Article 33(3) PCT. Here, D1 is considered the closest prior art. This document discloses (the references in parentheses referring to this document): glycated insulin as a biomarker of diabetes (figure 7).
- 3.1.2 The additional technical feature of claim 1 over D1 is that glycated insulin is measured at two time-points and compared.
- 3.1.3 The technical effect associated with this is that an increased severity can be diagnosed if the concentration of glycated insulin is less at the second time-

point.

- 3.1.4 The problem to be solved by the present invention may therefore be regarded as the provision of a method for monitoring progression of diabetes towards an increased severity.
- 3.1.5 The solution to this problem is to measure and compare glycated insulin levels at two different time-points.
- 3.1.6 The solution to the problem is not suggested or derivable in an obvious way from the prior art. Indeed, the finding that glycated insulin levels decrease with increased severity of diabetes is completely the opposite to what would be expected from the disclosure of D1. Therefore, the subject-matter of claim 1 is inventive in the sense of Article 33(3) PCT.

- 3.2 The subject-matter of independent claims 2 and 3 is also considered inventive (Article 33(3) PCT), since it is additionally shown that glycated insulin levels are higher in people who are either at risk of diabetes or in the early stages of the disease when plasma glucose levels are still normal. This finding is surprising and unexpected, since previously it would have been assumed from the disclosure of D1 that glycated insulin levels would closely correlate with plasma glucose levels, which indicate the presence of diabetes. Since the subject-matter of claims 4-11 also contains this special technical feature, their subject-matter is likewise considered inventive (Article 33(3) PCT).

#### 4 INDUSTRIAL APPLICABILITY

- 4.1 The subject-matter of claims 1-11 is industrially applicable in the field of *in vitro* diagnosis of diabetes and the distinguishing of the different disease stages thereof (Article 33(4) PCT).

1     **Claims**

2

3     1.    A method of monitoring the progression of  
4           diabetes from a first timepoint to a later  
5           timepoint, said method comprising the steps  
6               providing a first biological sample  
7               obtained at the first timepoint,  
8               measuring the concentration of glycated  
9               insulin in said biological sample,  
10              providing a second biological sample  
11              obtained at the later timepoint,  
12              measuring the concentration of glycated  
13              insulin in said second biological sample,  
14              determining the difference in  
15              concentration of glycated insulin between  
16              the first and second biological samples,  
17              wherein a lower concentration at the  
18              second timepoint is indicative of  
19              increased disease severity and/or loss of  
20              control of blood glucose.

21

22     2.    A method of early diagnosis of diabetes in an  
23           individual, the method comprising the steps  
24           providing a biological sample in which glucose  
25           levels are within a normal range from said  
26           individual,  
27           measuring the concentration of glycated insulin  
28           in the biological sample,  
29           wherein the presence of glycated insulin at a  
30           concentration greater than a predetermined minimum  
31           is indicative of the presence of diabetes.

32

- 1 3. A method of predicting the onset of diabetes in  
2 an individual, the method including the steps  
3 of;  
4 providing a biological sample from said  
5 individual,  
6 measuring the concentration of glycated insulin  
7 in the biological sample,  
8 wherein the presence of glycated insulin at a  
9 concentration greater than a predetermined  
10 minimum is indicative of predisposition to  
11 diabetes.  
12
- 13 4. The method according to claim 3, wherein the  
14 concentration of glucose in the biological  
15 sample is within the normal range.  
16
- 17 5. The method according to claim 2 or claim 4  
18 wherein the normal range of glucose is less than  
19 11.1 mmol/l in a random plasma sample.  
20
- 21 6. The method according to any one of claims 2 to 5  
22 wherein said predetermined minimum concentration  
23 is the concentration of glycated insulin  
24 measured in a sample from the same individual at  
25 an earlier timepoint.  
26
- 27 7. The method according to any one of claims 2 to  
28 6, wherein said predetermined minimum  
29 concentration of glycated insulin in a non  
30 fasted sample is at least 20 pmol/l.  
31

- 1 8. A method as claimed in any preceding claim  
2 wherein glycated insulin in the sample is  
3 measured by means of radioimmunoassay (RIA).  
4
- 5 9. Use of glycated insulin, as a predictive marker  
6 for glucose intolerance and/or diabetes.  
7
- 8 10. Use of glycated insulin as a predictive marker  
9 for prediabetes or to predict the onset of  
10 diabetes.  
11
- 12 11. An *in vitro* assay method for detecting diabetes  
13 or the predisposition to diabetes by determining  
14 the presence of glycated insulin in a biological  
15 sample, in which glucose levels are normal, said  
16 assay method comprising the steps:  
17 providing a biological sample;  
18 determining whether the concentration of  
19 glycated insulin in the biological sample is at  
20 least 20 pmol/l;  
21 wherein the presence of glycated insulin at a  
22 concentration greater than 20 pmol/l is  
23 indicative of diabetes or predisposition to  
24 diabetes.  
25  
26